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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/669,187	09/25/2000	Arthur M. Krieg	C1039/7035 (HCL/MAT)	2999

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EXAMINER	
BLANCHARD, DAVID J	
ART UNIT	PAPER NUMBER
1643	
MAIL DATE	DELIVERY MODE
11/26/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/669,187	KRIEG ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *121-142* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *121-142* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-120 are cancelled.

2. Claim 121 and 139-142 have been amended.

3. Claims 121-142 are under consideration.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Rejections Maintained

5. The rejection of claims 121-142 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement as introducing new matter is maintained. The claims contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The response filed 8/4/2008 reviews the legal requirements for satisfying the written description requirement, with which the Examiner takes no issue. Applicant states that the claims are drawn to methods for increasing the responsiveness to a cancer therapy by administering an immunostimulatory oligonucleotide comprising the sequence of SEQ ID NO:246 and particular cancer medicament. At pp. 7-8 Applicant references various portions of the specification, which applicant asserts provide adequate written support for the instantly claimed methods. Applicant maintains that the as filed specification provides the relevant identifying characteristics of the genus in that the claimed immunostimulatory oligonucleotides all require the sequence of SEQ ID NO:246. Applicant refers to SEQ ID Nos:305 and 429, which are each 30 nucleotides in length and differ from each other in the flanking sequence outside of the core sequence defined by SEQ ID NO:246. Applicants' arguments have been fully considered but are not found persuasive. The claims still encompass an extremely large genus of immunostimulatory oligonucleotides that comprise the

consensus sequence of SEQ ID NO:246 and may contain additional sequence up to 40 or up to 100 nucleotides in length of the claimed method. The examiner maintains that the disclosure of SEQ ID Nos: 262, 273, 300, 305, 352, 412, 413, 429 and 891 are not representative of the genus because SEQ ID Nos:262, 273, 300, 352, 412, 413 and 891 are identical to SEQ ID NO:246 and although SEQ ID NO:305 comprises 5 additional T's at the 3' end and SEQ ID NO:429 comprises the additional sequence ttgtcgtt at the 3' end, Applicants' reliance on the description of a SEQ ID Nos:305, 429 and the generic disclosure of poly A and poly T tails are not representative of the entire genus because the genus is highly variable, inclusive to immunostimulatory oligonucleotides of varying lengths and having different chemical structures or sequences, which were not clearly disclosed or contemplated in the as filed application. Applicant has not pointed to a single immunostimulatory oligonucleotide that comprises SEQ ID NO:246 and is 35, 40, 50, 70, 90, 93, or 100 nucleotides in length and comprising just any nucleotide sequence in addition to SEQ ID NO:246 that function equivalently. Applicant is critical of the examiners remarks that the immunostimulatory nature of the claimed genus may be negatively impacted by flanking sequences. In response, the specification teaches that the sequence, number and spacing of individual CpG motifs contribute to the immunostimulatory activity of a CpG phosphorothioate ODN (see page 148). At page 152, the specification teaches that the immunostimulatory activity of ODNs without CpG motifs was negative or weak compared to CpG ODNs and ODNs with non-optimal CpG motifs were less active than ODNs containing CpG motifs flanked by two 5' purines and two 3' pyrimidines (see page 152, lines 10-17). Again, not all CpG's function equivalently and when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one or a limited number of species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]." See *Enzo Biochem*, 323 F.3d at 966, 63

USPQ2d at 1615; *Noelle v. Lederman*, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004)("[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated."). There is insufficient written support for the subgenus of immunostimulatory oligonucleotides "comprising" up to 100 nucleotides or "comprising" 24-40 nucleotides as the as filed disclosure contains no description of the sequences contained therein and based on the limited disclosure of SEQ ID NO:246, one of skill in the art would reasonably conclude that the disclosure does not provide a representative number of species to describe the presently claimed sub-genus. Additionally, the as filed specification only discloses SEQ ID NO:246 as unmethylated and having a phosphorothioate backbone modification. While SEQ ID Nos:262, 273, 300, 352, 412, 413 and 891 would support the claimed method comprising SEQ ID NO:246 wherein the C in each recited CG is unmethylated, and comprising at least one backbone modification, base claim 121 does not require any backbone modification. Even if claim 121 required at least one backbone modification, the claims would still lack adequate written support for the claimed genus of immunostimulatory oligonucleotides that comprise SEQ ID NO:246 as discussed supra. Again, Applicants reliance on a general disclosure, e.g., pp7-8 of the response filed 8/4/08, and possibly a single species (i.e., immunostimulatory oligonucleotide SEQ ID NO:246) has not provided sufficient direction and guidance to the features currently claimed. It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05.

Applicant maintains that the art was sufficiently developed at the time of filing that one of ordinary skill in the art would recognize that flanking sequences could be added to a known immunostimulatory sequence without negative impact to the immunostimulatory activity, citing US Patents 6,194,388, 6,207,646, 6,239,116, 7,271,156 and 7,402,572 for support. Applicant states that the

Examiner's position is wholly inconsistent with the Patent Office's position, as evidenced by the granted claims of the above patents, all of which were deemed adequately described by specifications similar to the instant specification. With respect to US Patents 6,194,388, 6,207,646, 6,239,116, 7,271,156 and 7,402,572, Applicant is reminded that each case is examined on it own merits and the examiner is precluded from commenting on issued US Patents under 35 USC 282. It is noted that none of the claims in the cited US Patents are drawn to the cancer therapy methods recited in the instant claims comprising administering an immunostimulatory oligonucleotide from the subgenus of immunostimulatory oligonucleotides comprising SEQ ID NO:246 and carboplatin, paclitaxel, doxorubicin, cisplatin or gemcitabine. Thus, the relevance of US Patents 6,194,388, 6,207,646, 6,239,116, 7,271,156 and 7,402,572 to the facts of the instant new matter rejection are not clear and there is nothing inconsistent with the Examiners' position on the issue of new matter in the instant rejection, given the facts before the examiner. The relevant issue before the examiner is whether the instant disclosure, as filed, provides adequate written support for the currently claimed limitations.

Applicant also states that the claimed immunostimulatory oligonucleotide in combination with any of the recited anti cancer therapies. Applicant notes that the specification places particular emphasis on the immunostimulatory oligonucleotide of SEQ ID NO:246. Applicant also notes that the specification explicitly discloses carboplatin, paclitaxel, doxorubicin, cisplatin and gemcitabine and therefore, the specification provides adequate support for the combination of immunostimulatory nucleic acids with each of these anti-cancer therapies. Applicant points to various pages in the specification for support. Applicants' arguments have been fully considered but are not found persuasive. Again, Applicants' reliance on a generic disclosure of numerous oligonucleotides and numerous chemotherapeutic agents (e.g., see pg. 15-16) does not provide adequate direction or guidance to the currently claimed limitations. The fact that carboplatin, paclitaxel, doxorubicin, cisplatin and gemcitabine are explicitly

disclosed, does not provide adequate guidance or direction to selecting the claimed combination of SEQ ID NO:246 or the subgenus of immunostimulatory oligonucleotides that "comprise" SEQ ID NO:246 in combination with carboplatin, paclitaxel, doxorubicin, cisplatin, gemcitabine or even *carboplatin and paclitaxel* (e.g., carboplatin and "another cancer medicament") for the treatment of cancer as opposed to the selection of any of the other possible combinations of chemotherapeutic agents, immunotherapeutic agents or cancer vaccines disclosed. As *Ruschig* makes clear, one cannot disclose a forest in the original application, and then later pick a tree out of the forest and say "here is my invention." In order to satisfy the written description requirement, the blaze marks directing the skilled artisan to that tree must be in the originally filed disclosure. *See id.* at 994-95, 154 USPQ at 122; *Fujikawa,* 93 F.3d at 1570-71, 39 USPQ2d at 1905; *Martin v. Mayer*, 823 F.2d 500, 505, 3 USPQ2d 1333, 1337 (Fed. Cir. 1987). Further, the as filed disclosure does not provide adequate written support for a method of increasing the responsiveness to a cancer therapy comprising administering an immunostimulatory oligonucleotide comprising unmethylated SEQ ID NO:246 and carboplatin and administering another cancer medicament (e.g., claim 131). The disclosure of "other cancer medicaments" would not have led the skilled artisan to administer such in combination with SEQ ID NO:246 and carboplatin. Again, where in the as filed disclosure is it contemplated that *carboplatin and another cancer medicament* were intended to be used with SEQ ID NO:246 or the subgenus of immunostimulatory sequences that "comprise" SEQ ID NO:246 in the treatment of non-small cell lung cancer?

The present application does not provide adequate written description for the subgenus of immunostimulatory sequences that "comprise" SEQ ID NO:246, or the particular combinations of said sequences and carboplatin, paclitaxel, doxorubicin, cisplatin, or gemcitabine as presently claimed from the myriad of possibilities encompassed by the broad disclosure (e.g., Table A and pp. 15-16) and there is no guidance or direction that the particular combinations presently claimed should be made rather than any of the others which could also be made.

Similar to *In re Smith*, the present claims are drawn to a various subgenus's of immunostimulatory oligonucleotides that "comprise" SEQ ID NO:246 and a particular chemotherapeutic agent(s), which are not adequately supported or described in applicants' generic disclosure of an immunostimulatory oligonucleotide in combination with a chemotherapeutic agent, an immunotherapeutic agent, or a cancer vaccine (e.g., see pp. 15-16), or in the disclosure of a single or limited species, i.e., unmethylated SEQ ID NO:246 comprising a phosphorothioate backbone. Similar to the facts in *Fujikawa v. Wattanasin*, where the Court found that a subgenus of a parent compound was not adequately described by disclosure of the parent compound itself, the disclosure of the immunostimulatory oligonucleotide SEQ ID NO:246 (i.e., the parent compound) does not provide written support for the subgenus of immunostimulatory oligonucleotides that are 24-40 nucleotides in length, or up to 100 nucleotides in length and comprise SEQ ID NO:246.

For these reasons and those already of record the rejection is maintained.

6. The rejection of claims 121-142 under 35 U.S.C. 103(a) as being unpatentable over Wagner et al (US 2004/0235778 A1, 5/14/1998) in view of Maxwell et al (Seminars in Oncology Nursing, 8(2):113-123, May 1992) is maintained.

The response filed 8/4/2008 states Wagner teaches that GM-CSF/IL5 are "dispensable for hematopoiesis" and applicant asserts that Wagner et al teaches that CpG are immunostimulatory but that they act through a different mechanism than by induction of GM-CSF. Applicant argues that Maxwell teaches that GM-CSF is effective for minimizing myelosuppression. Applicant concludes that there would have been no motivation to combine Wagner et al and Maxwell et al since Maxwell did not suggest the use of CpG ODNs, and instead taught the use of growth factors such as GM-CSF and Wagner et al taught the distinctions

between immune induction by CpG ODNs and by growth factors such as GM-CSF. Applicants' arguments have been fully considered but are not found persuasive. With respect to applicants' argument that Wagner et al does not disclose coadministering an immunostimulatory oligonucleotide corresponding to SEQ ID NO:246 with carboplatin, paclitaxel, doxorubicin, cisplatin or gemcitabine and applicants' argument that Maxwell et al does not teach combining an immunostimulatory oligonucleotide with any of these chemotherapeutic agents, applicant is reminded that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). While Maxwell et al recognizes the art known use of GM-CSF to reduce or minimize the degree and duration of myelosuppression during chemotherapy, it is reiterated that Maxwell et al teach that chemotherapy-induced myelosuppression is the most common dose limiting and potentially fatal complication of cancer treatment and myelosuppression, characterized by neutropenia and thrombocytopenia are common with chemotherapy treatments and decrease the body's immune barriers and Maxwell teach the chemotherapeutic agents carboplatin, paclitaxol (taxol), cisplatin, 5-fluorouracil and doxorubicin, among others, and Wagner et al teach a method of treating cancer including non-small cell lung cancer in a human subject having thrombocytopenia (i.e., myelosuppression) as a consequence of chemotherapy comprising administering by injection the immunostimulatory oligonucleotide of SEQ ID NO:80 (identical to the immunostimulatory oligonucleotide of SEQ ID NO:246) for inducing hematopoiesis of specific immune cells such as platelets and erythroblasts. Therefore, one of ordinary skill in the art would have been motivated by the goal of reducing chemotherapy-induced myelosuppression in cancer patients, to administer by injection the immunostimulatory oligonucleotide of SEQ ID NO:80 in combination with one or more of carboplatin, paclitaxol (taxol), cisplatin, 5-fluorouracil and/or doxorubicin, in order to induce hematopoiesis of immune cells

such as platelets and erythroblasts, thereby countering the dose-limiting toxicities associated with chemotherapy in cancer patients. Further, one of ordinary skill in the art would have had a reasonable expectation of success in making the above modification in view of the teachings of Wagner et al, providing evidence that the combination of a chemotherapeutic agent and an immunostimulatory oligonucleotide reduces the loss of platelets compared to chemotherapeutic agent alone (see Fig. 13). The idea that one of ordinary skill in the art would only look to the use of growth factors such as GM-CSF for reducing myelosuppression and would not recognize the advantages of using the immunostimulatory oligonucleotide of SEQ ID NO:80 (identical to the immunostimulatory oligonucleotide of SEQ ID NO:246) for inducing hematopoiesis of specific immune cells such as platelets and erythroblasts in cancer patients having thrombocytopenia (i.e., myelosuppression), thereby reducing myelosuppression as taught by Wagner et al, makes little sense. "A person of ordinary skill in the art is also a person of ordinary creativity, not an automaton." KSR International Co. v. Teleflex Inc., 550 U.S. ___, ___, 82 USPQ2d 1385, 1397 (2007). "[I]n many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle." Id. Office personnel may also take into account "the inferences and creative steps that a person of ordinary skill in the art would employ." Id. at ___, 82 USPQ2d at 1396. Further, "the prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed…." *In re Fulton*, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004). Additionally, applicants' distinction between GM-CSF and CpG ODNs is curious in view of applicants' publication (Krieg A. M. BioDrugs, 10(5):341-346, 1998, cited on PTO-892 mailed 8/9/06), which shows that CpG's activate a variety of cells and cellular responses including activation of monocyte-derived cells such as macrophages and dendritic cells, which in-turn release GM-CSF among other cytokines and growth factors (e.g., see Fig 1).

Applicant also argues that the limitation "increasing the responsiveness to a cancer therapy" is not taught in the cited references. Applicant argues that in *Ex Parte Obiaya* and *In re Wiseman* the issue was one of unexpected and unclaimed properties, while the issue in the instant case is that the combination of the references does not yield all of the explicitly recited claim limitations. Applicant alleges that the examiner's approach of reading the preamble out of the claims is legally incorrect. Applicants' arguments have been fully considered but are not found persuasive. In response to applicant's arguments, the recitation "increasing the responsiveness to a cancer therapy" has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951). Further, even if the preamble were given patentable weight, as discussed supra, the method for treating cancer or non-small cell lung cancer in a human patient comprising administering by injection the immunostimulatory oligonucleotide of SEQ ID NO:80 (identical to SEQ ID NO:246) in combination with one or more of carboplatin, paclitaxel, cisplatin, 5-fluorouracil and/or doxorubicin in an effective amount to treat the cancer as taught by Maxwell et al and Wagner et al, would necessarily "increase the responsiveness to a cancer therapy". The fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. *In re Wiseman*, 596 F.2d 1019, 201 USPQ 658 (CCPA 1979). See MPEP 2145 II.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references and the rejection is maintained.

7. No claim is allowed.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832.

The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR

system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David J. Blanchard/
Primary Examiner, A.U. 1643